2010 Military Health System Conference

Advances in Tissue Regeneration

Sharing Knowledge: Achieving Breakthrough Performance

COL Bob Vandre, DDS, MS

26 & 27 JAN 2010

Armed Forces Institute of Regenerative Medicine

Report Documentation Page

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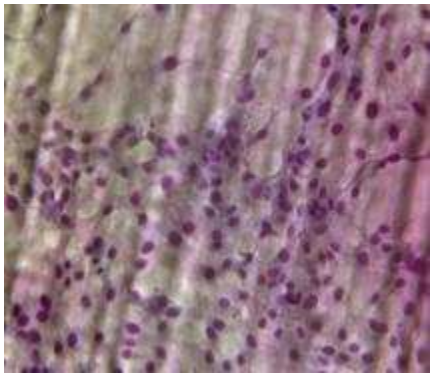
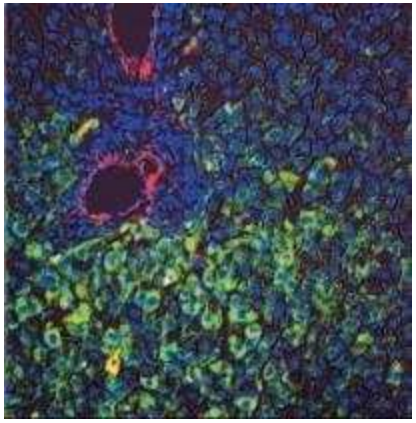
1954, First organ transplant, Boston

Today, Increasing problem: tissue and organ shortage and rejection

What is Regenerative Medicine?



Tissue Engineering and Biomaterials

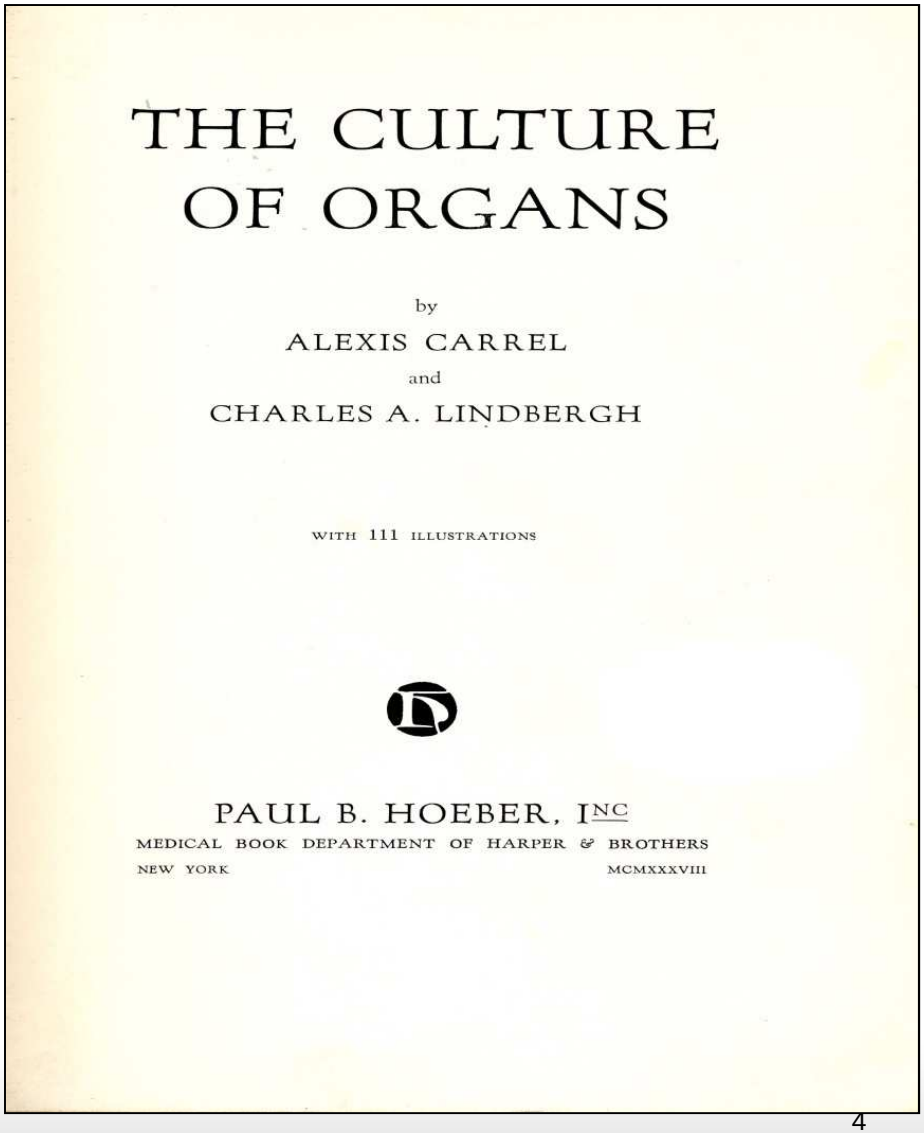


Cellular Therapies

Medical Devices and Artificial Organs

Regenerative Medicine / Tissue Engineering

- Based on the field of cell transplantation (started in 1930s)
- First clinical application: engineered skin for burn patients, 1981



THE CULTURE
OF ORGANS

by
ALEXIS CARREL
and
CHARLES A. LINDBERGH

WITH 111 ILLUSTRATIONS

PAUL B. HOEBER, INC
MEDICAL BOOK DEPARTMENT OF HARPER & BROTHERS
NEW YORK MCMXXXVIII

Regenerative Medicine / Tissue Engineering

- A field of research for over 60 years. Why so few clinical advances?
  - Inability to expand cells in vitro
  - Inadequate biomaterials
  - Inadequate vascularity

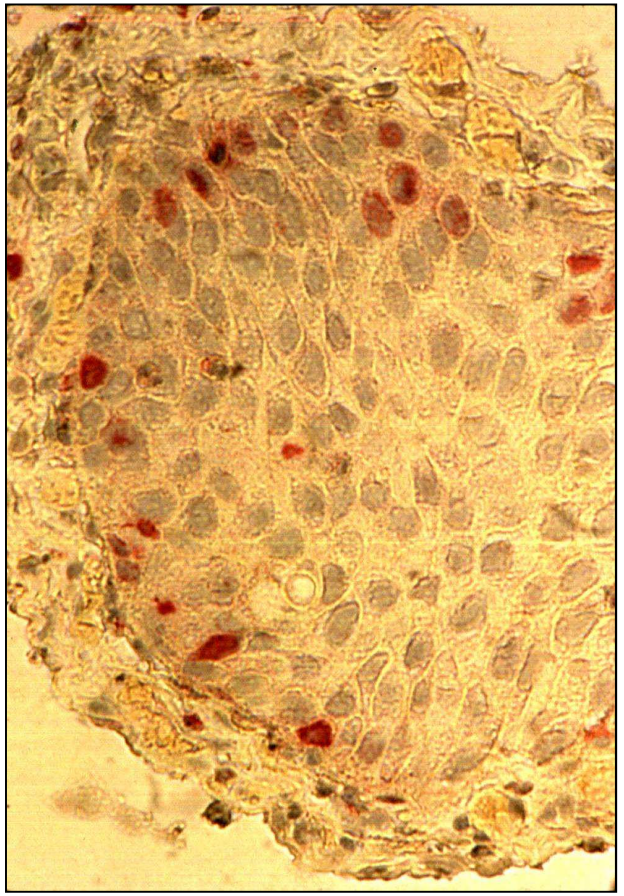
Progenitor Cells

1 cm^2

Day 1 (5 X 10^4 cells)

Day 60 (50 X 10^9 cells)

Enough cells to cover a football field



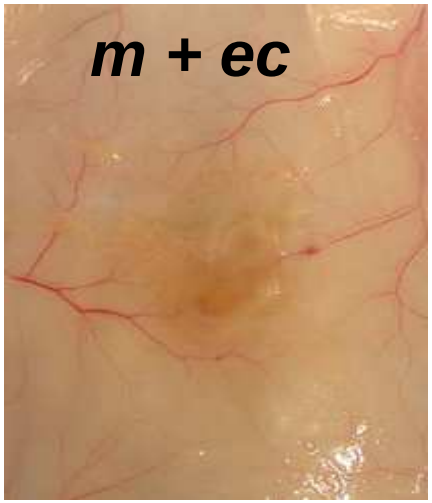
CELL DELIVERY VEHICLES

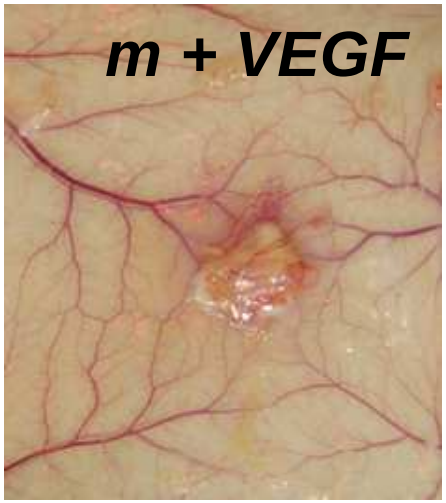
- **Biocompatibility**
  - **Cell attachment**
  - **Cell viability**
- **Degradation curves**
  - **Inflammatory responses**
  - **Biomechanical properties**
- **The scaffold should replicate the biomechanical and structural properties of the tissue being replaced.**

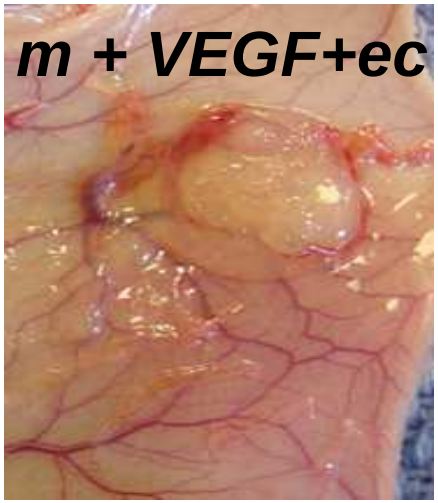
Scaffold in the shape of a human ear

Vascularity: Problem

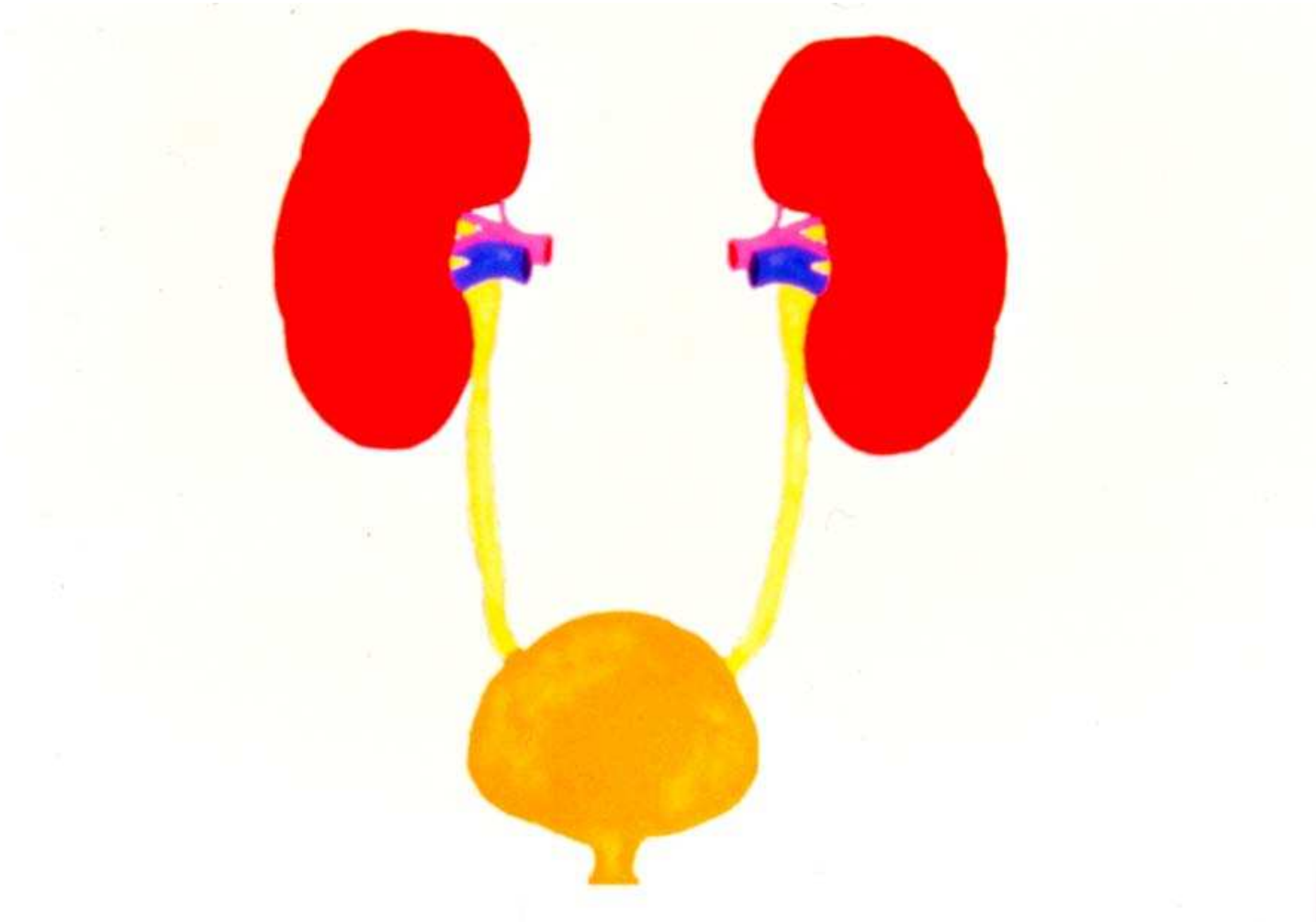
- Cells cannot be implanted in volumes greater than 3 mm3 (the size of a pencil eraser)
- Nutrition to the cells is limited (limited vascularity)



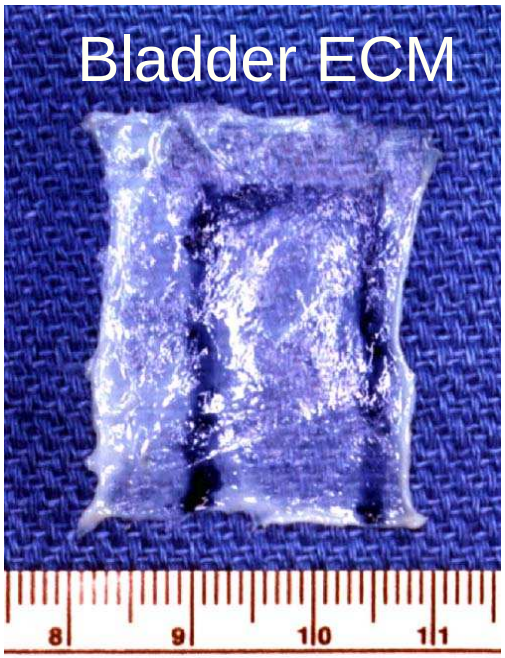


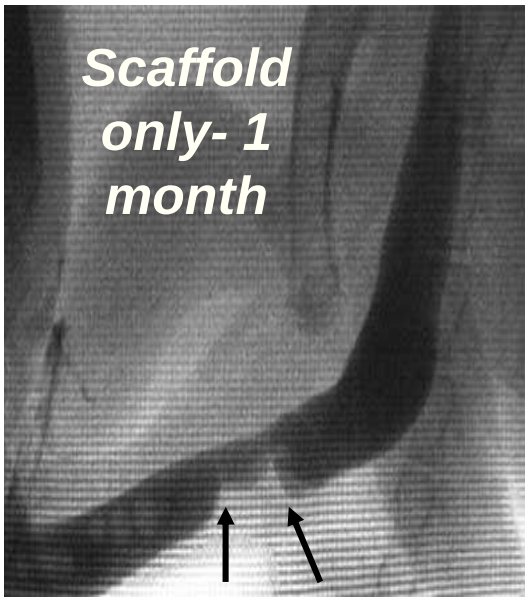


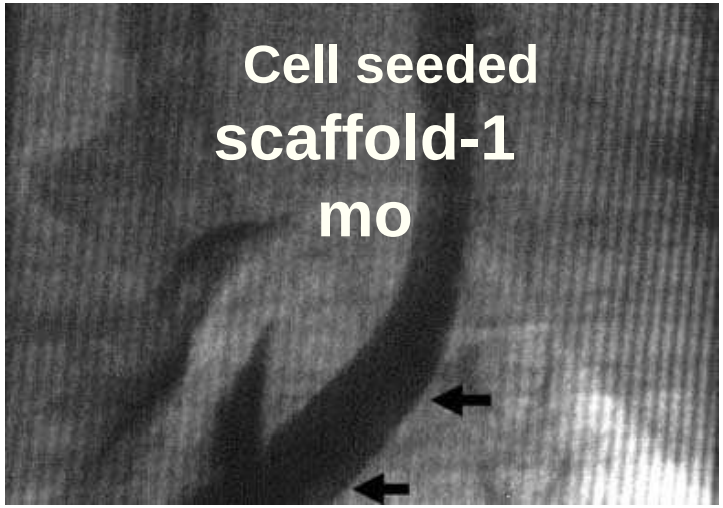
Urinary System

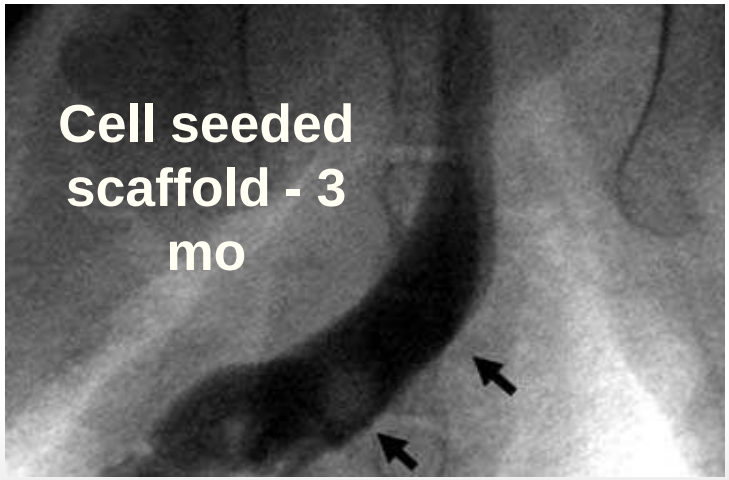


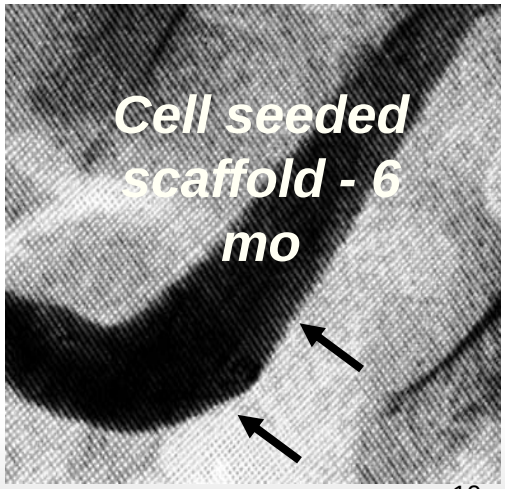
Engineered Urethras





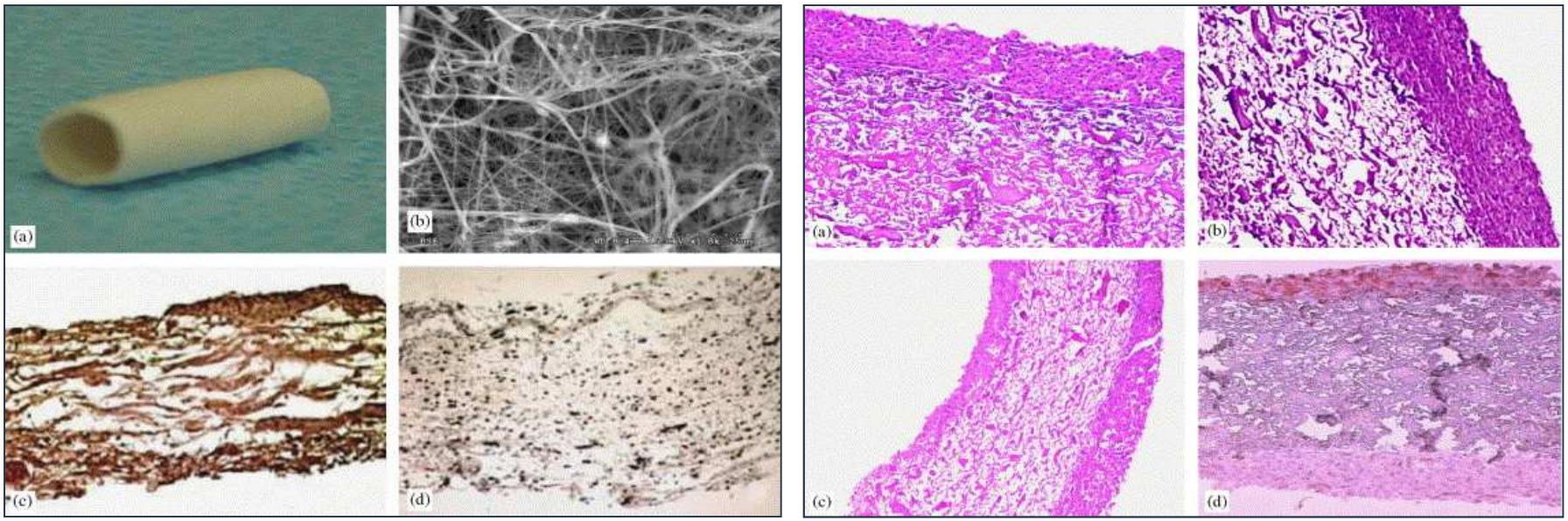






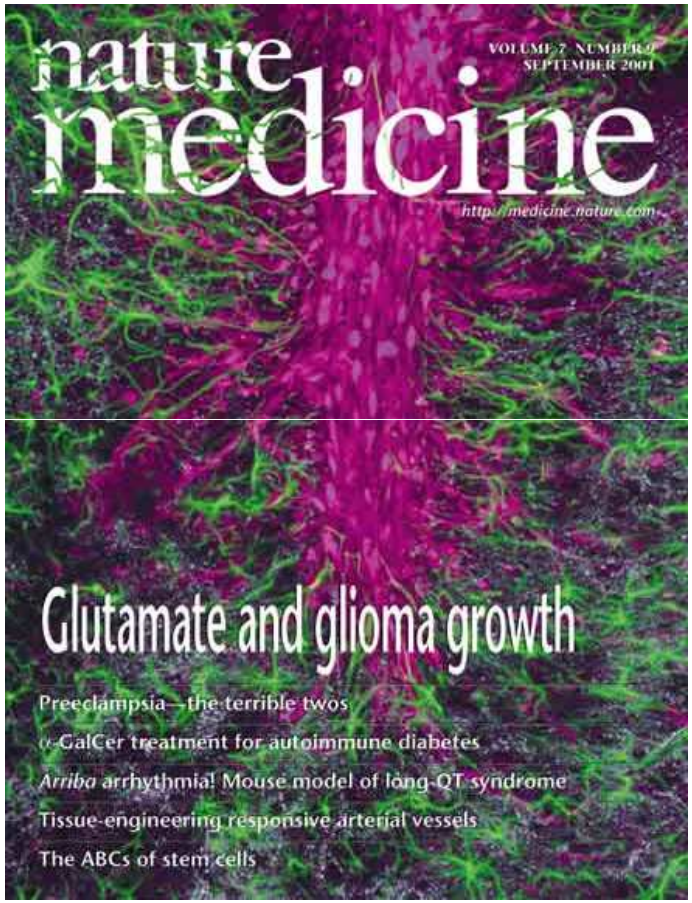
Fabrication of a vascular substitute

Electrospun nanofiber substrate, with endothelial and smooth muscle cells

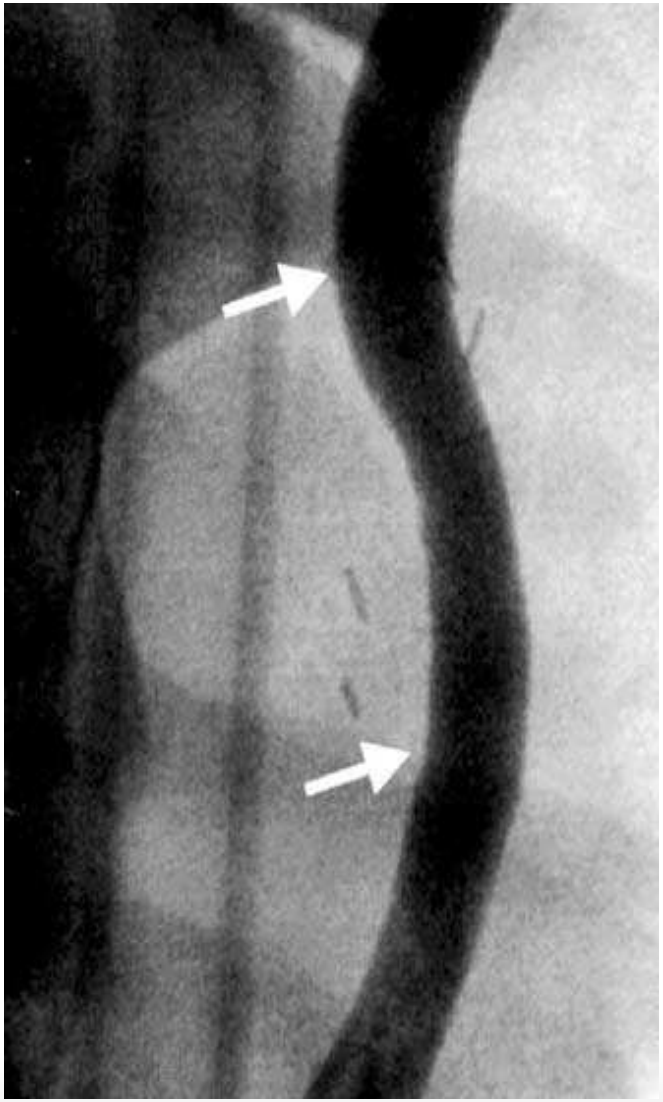


Stitzel et al., *Biomaterials*, 2005.

Tissue Engineered Arteries



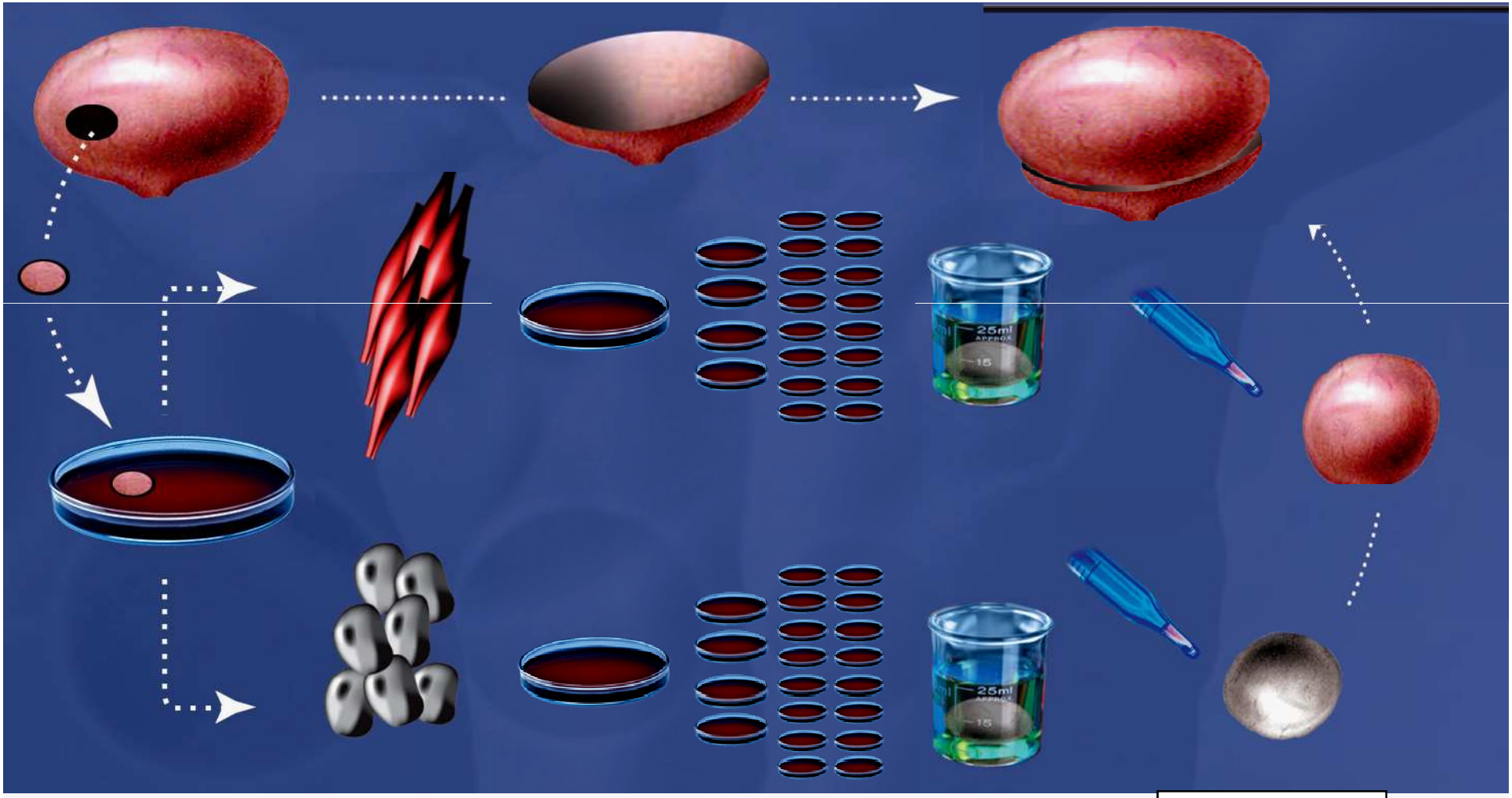
Kaushal et al



Engineered Artery

Native Artery

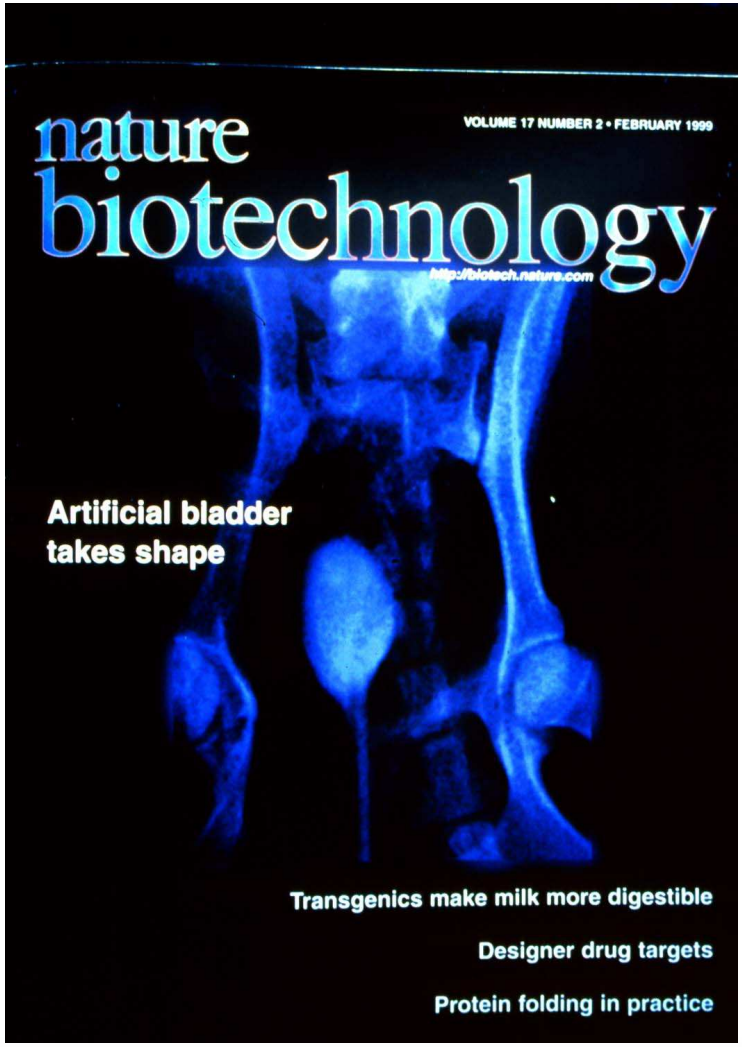
Creation of the First Engineered Organ: Bladder



6 weeks

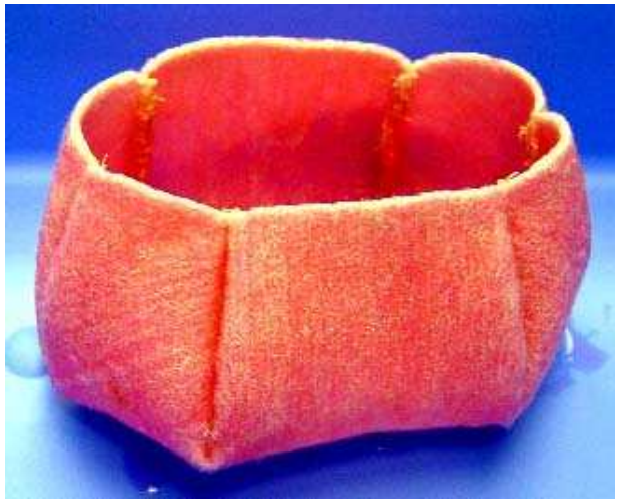
Clinical Studies

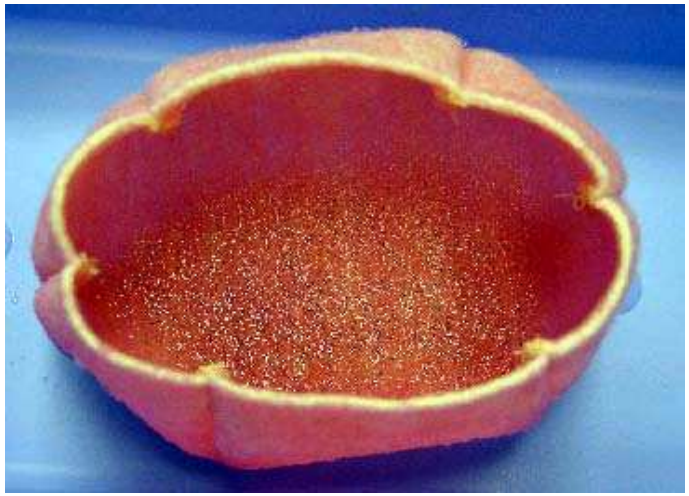
- Patients with high pressure /low capacity bladders
- All failed medical therapy and were considered candidates for bladder reconstruction

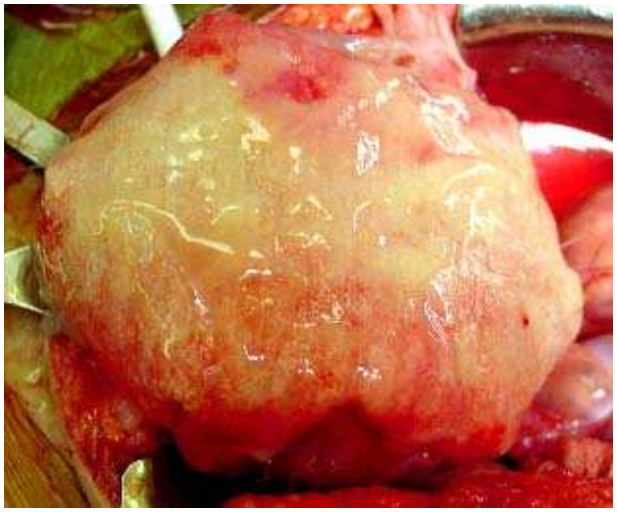


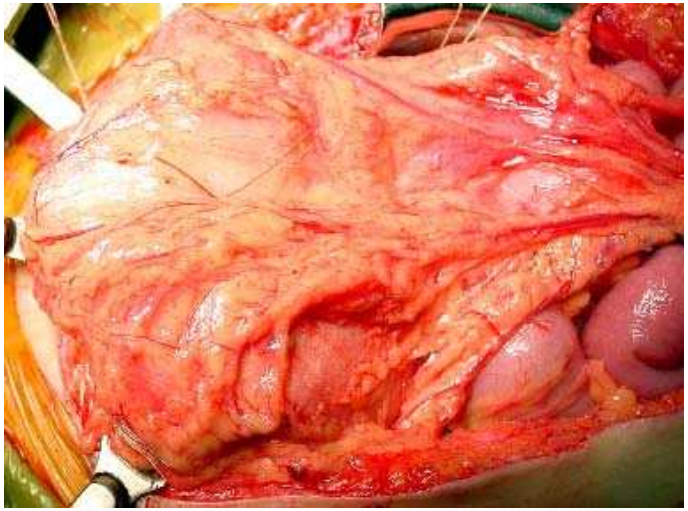
Oberpenning et al, 1999

Bioengineered Bladder

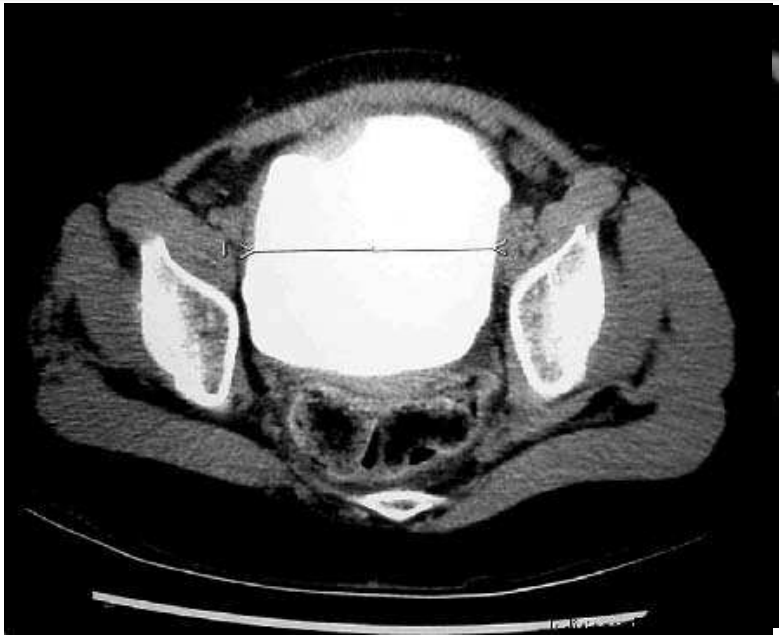


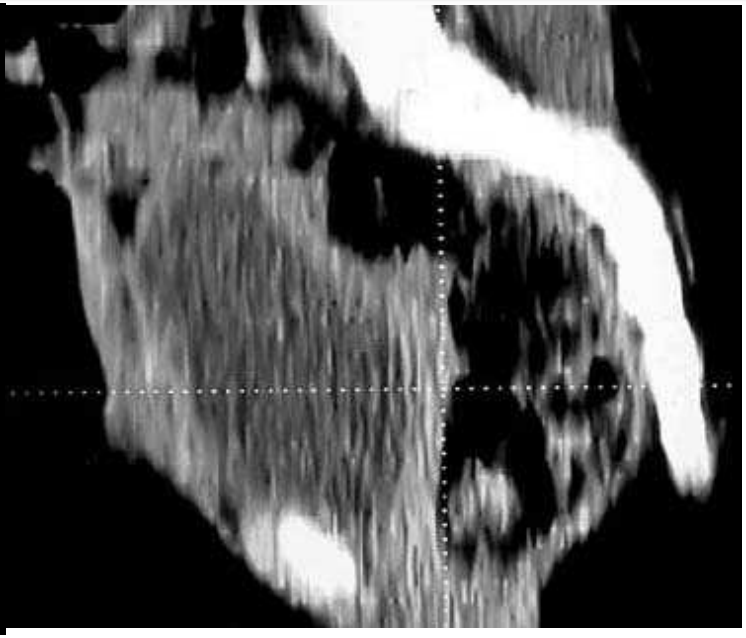


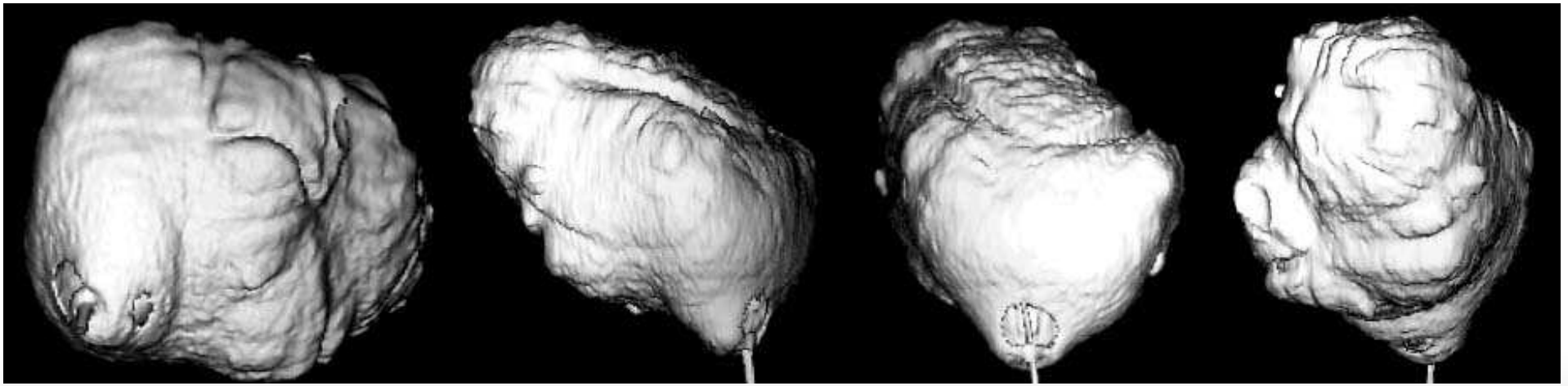




Bioengineered Bladder

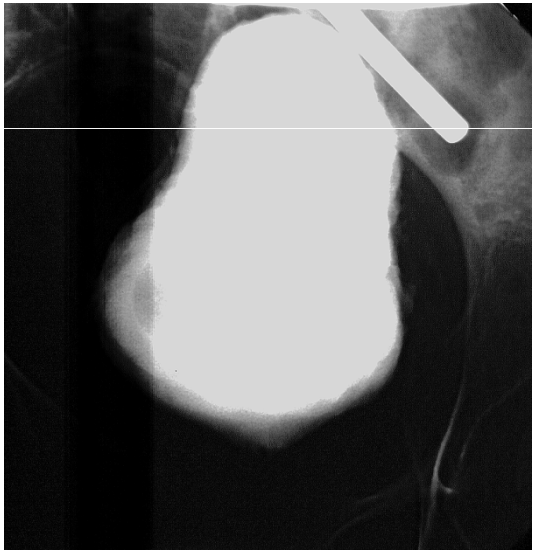




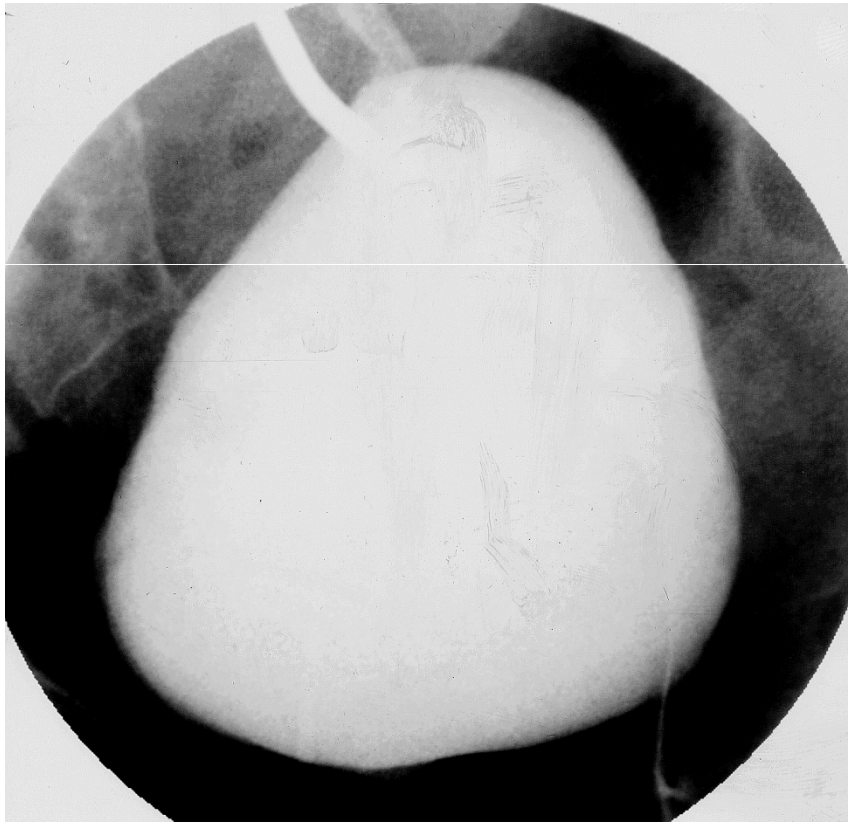


Bioengineered Bladder

Pre-Op



Post-Op



Bioengineered Bladder

THE LANCET

"**Tissue-engineered autologous bladders for patients needing cystoplasty**"

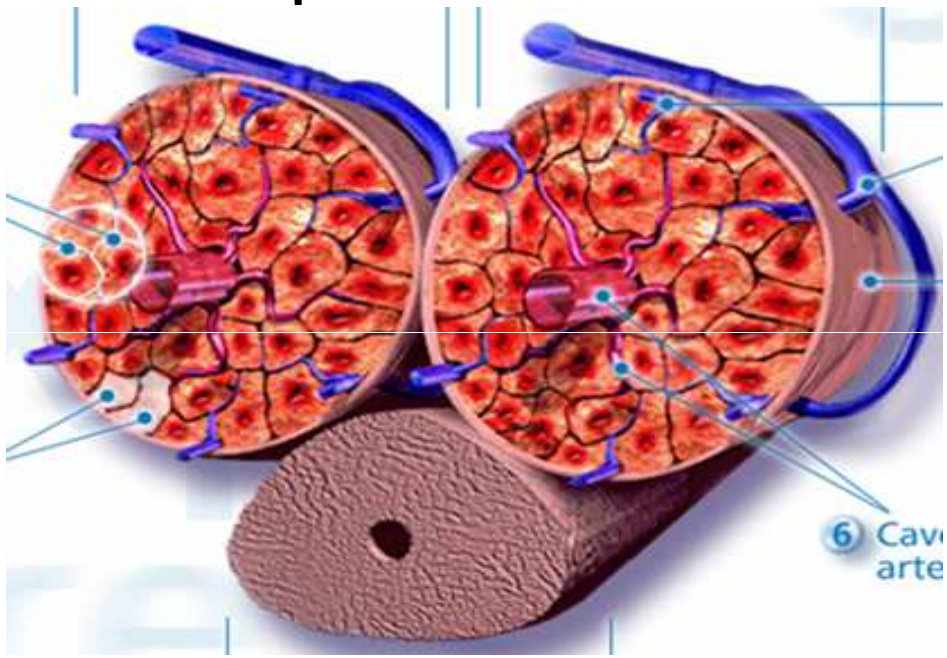
April 2006

Clinical Experience
Phase 1, 2 trials completed
Over 10 year follow-up
Work still in progress

Anatomy & Function of the Phallus

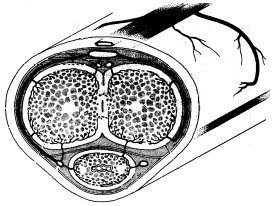
- Complex organ composed of skin, muscle, nerves, and blood vessels (arteries and veins)

Corpus cavernosum

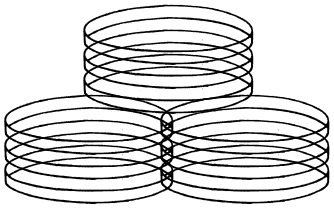


Corpus spongiosum

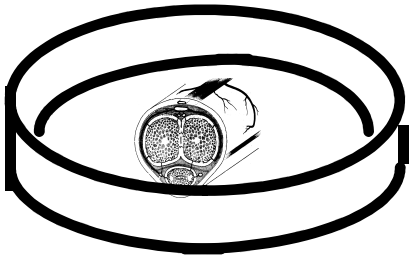
Penile Replacement: Study Overview



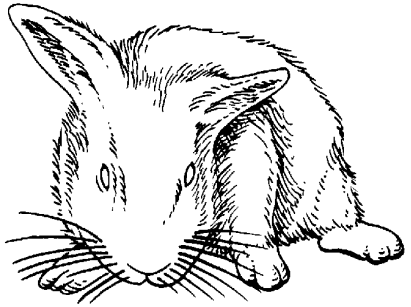
Autologous cavernosal cell harvest



Cells are grown and expanded



Cells are seeded on decellularized penile corpora matrices



Corporal tissue penile replacement

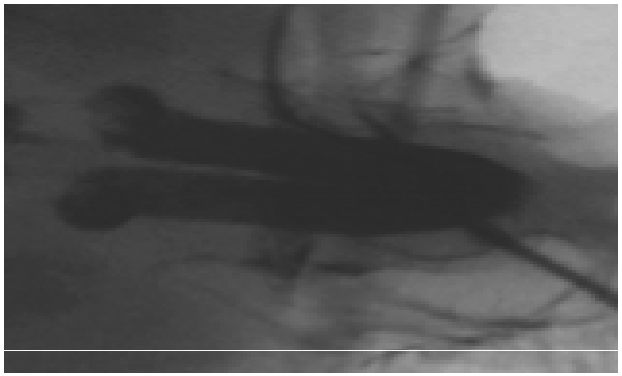
Retrieval of engineered corporal tissue

Analyses

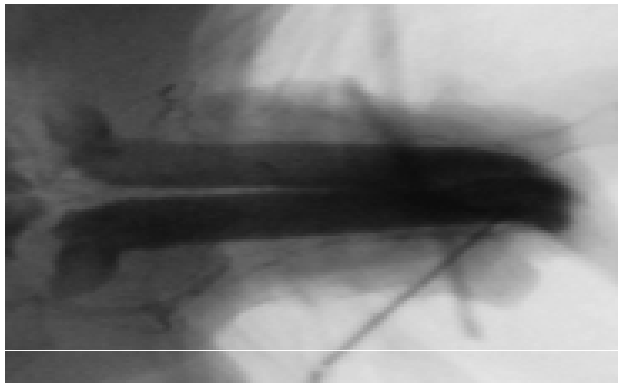
Engineered Phallus

Total Corpora Replacement, Cavernosography

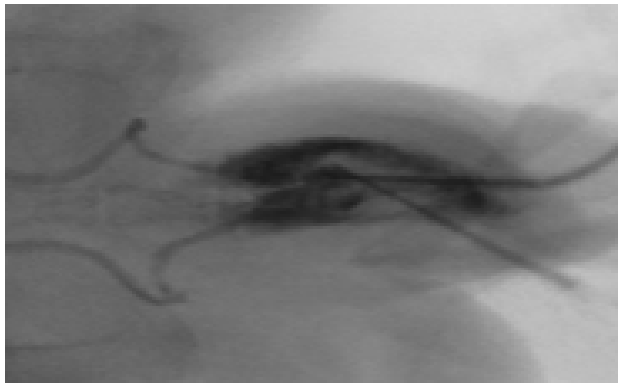
Native corpora



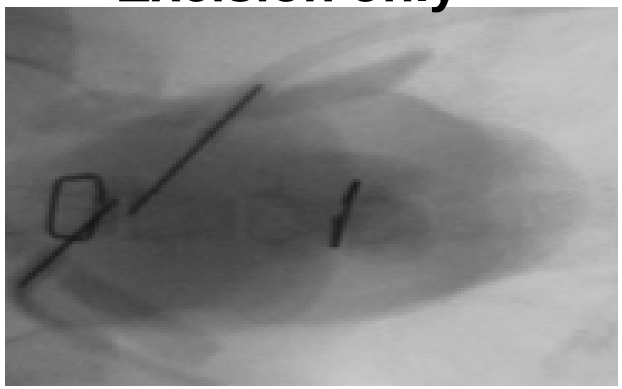
Matrix with cells



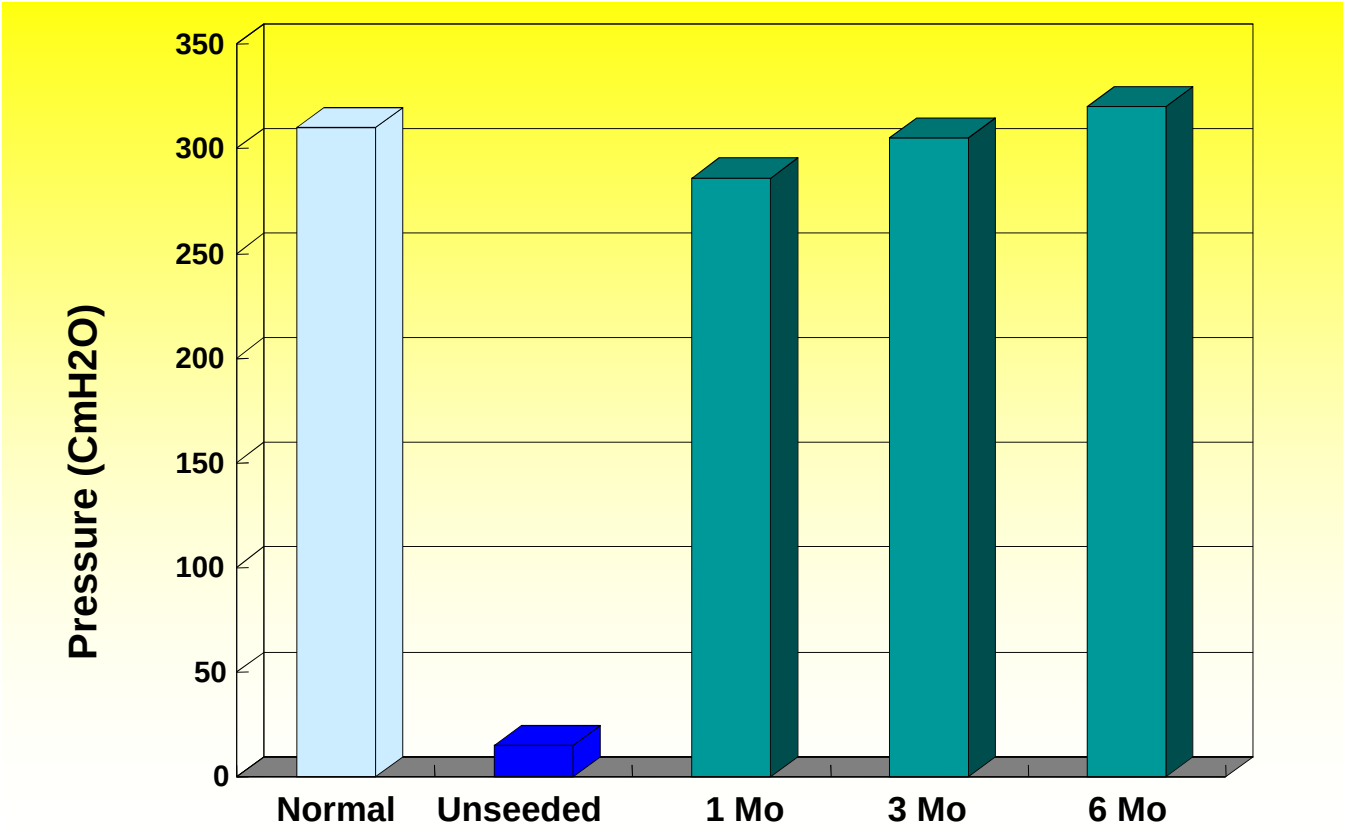
Matrix without cells



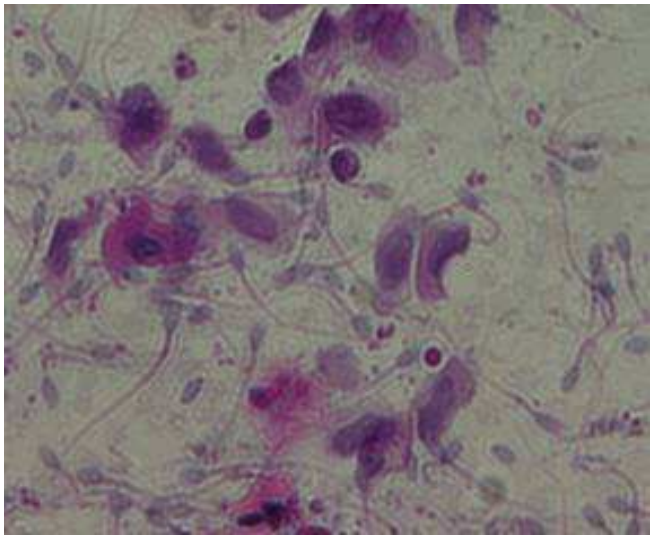
Excision only



Cavernosometry



Engineered phalluses are functional



Sperm in Vaginal swab

Bunnies

	Vaginal swab (+) / Pregnancy rate
Experimental (with Cells)	**33%**
Control (Without Cells)	**0%**

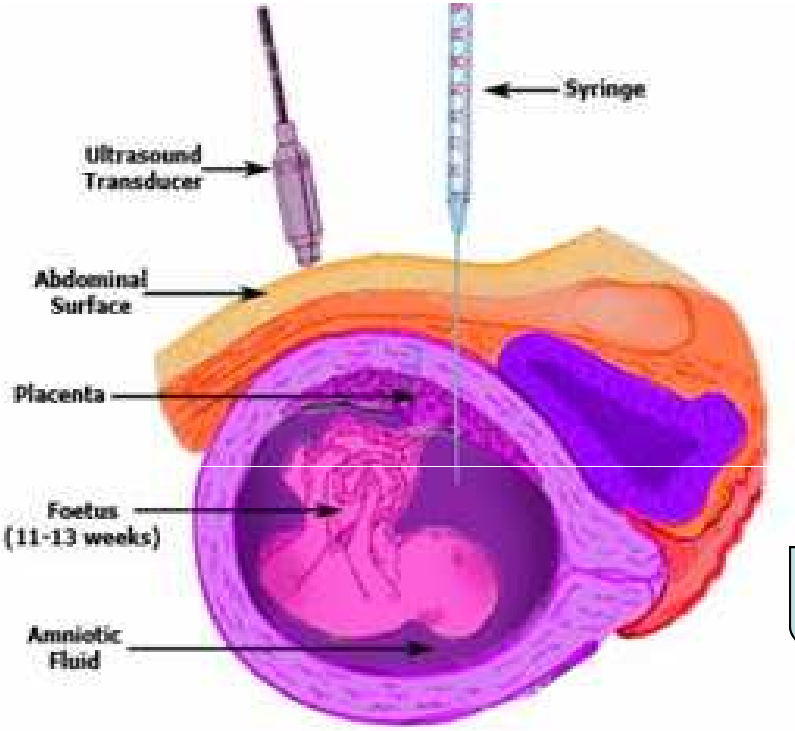
PNAS, Chen et al, 2009

Human Embryonic Stem Cells

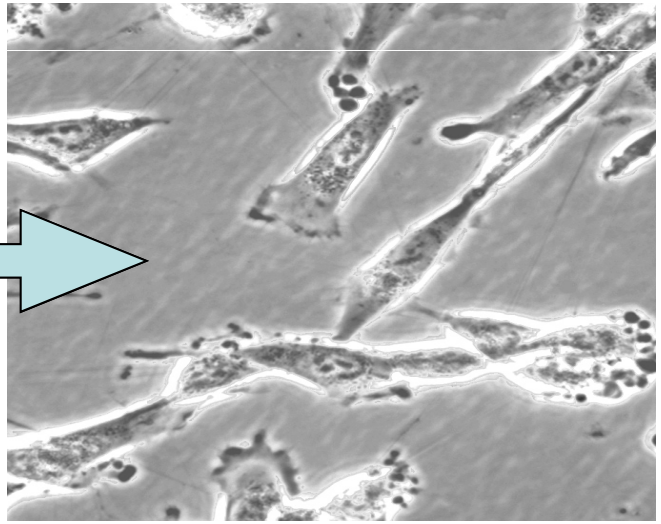
- Pro: very high replicative potential
- Con: tumor potential, issues with rejection

J. Thomson, 1998

Amniotic fluid and placental derived stem cells



- Pro: very high replicative potential, low tumor potential
- Con: issues with rejection



AFS cells

Stem Cell Characteristics

	Embryonic	IPS	Amniotic/ Placenta	Marrow/ Fat	Tissue Specific
Growth Potential	+++	+++	+++	+	++
Tumor Free			+++	+++	+++
Rejection Free		+++		+++	+++
Lineage Potential	+++	+++	++	+	+

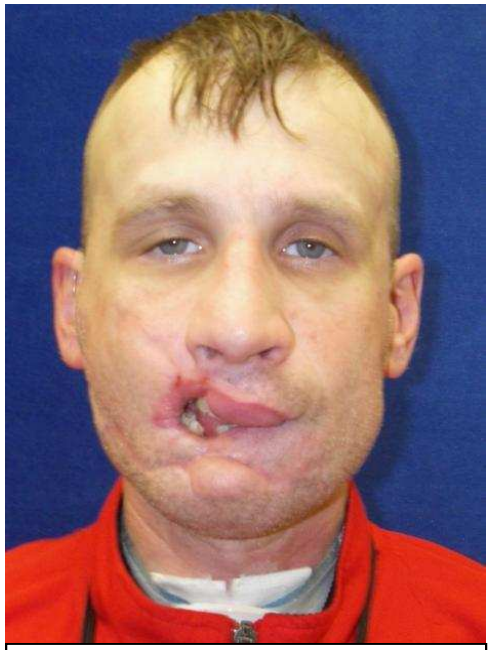
What is the Armed Forces Institute of Regenerative Medicine?

www.afirm.mil

- Two consortia working together with the US Army Institute of Surgical Research (230 scientists)
  - 27 Universities
  - 114 investigators – 30% of which are clinicians
  - 46 graduate students
  - 70 post-docs
- Total 5 yr funding of >$250M
  - $100M US Government funding from:
    - Army, Navy, Air force, VA, and NIH
  - $68M Matching funds from:
    - State governments, and participating universities
  - $109M in pre-existing research projects directly related to the deliverables of the AFIRM
    - From NIH, DARPA, Congressional plus-ups, NSF, philanthropy

Goal: *To Heal our Wounded Warriors*

Five Areas of Emphasis:



Cranio-Facial Reconstruction

Healing Without Scarring

Limb and Digit Salvage and Reconstruction

Compartment Syndrome

Burn Repair

www.afirm.mil

Our Partnership

www.afirm.mil

- **US Army Institute of Surgical Research**

- **Wake Forest – Pittsburgh**
  - The Wake Forest Institute for Regenerative Medicine (NC)
  - The McGowan Institute for Regenerative medicine (Univ. of Pittsburgh)
  - Allegheny Singer Research Institute
  - Carnegie Mellon University
  - Georgia Tech Univ
  - Institute for Collaborative Biotechnology (ICB) that includes UC Santa Barbara, MIT and Caltech
  - Oregon Medical Laser Center
  - Stanford University
  - Rice University
  - Tufts University
  - University of Texas Health Sciences Center-Houston
  - Vanderbilt University

- **Rutgers – Cleveland Clinic**
  - Rutgers /New Jersey Center for Biomaterials
  - Cleveland Clinic Foundation
  - Carnegie Mellon University
  - Case Western Reserve University
  - Dartmouth Hitchcock Medical Center
  - Massachusetts General Hospital / Harvard Medical School
  - Massachusetts Institute of Technology
  - Mayo Clinic College of Medicine
  - Northwestern University
  - State University of New York at Stony Brook
  - University of Cincinnati
  - University of Medicine and Dentistry of New Jersey
  - University of Pennsylvania
  - University of Utah
  - University of Virginia
  - Vanderbilt University

Top Publishing US Universities (2001-2007)

Stem Cells for Regenerative Medicine and Tissue Engineering

www.afirm.mil

US Rank	University	In AFIRM
1	Harvard	Y
2	MIT	Y
3	Univ. Pittsburgh	Y
4	Columbia Univ.	
5	Tufts	Y
6	Georgia Tech	Y
7	Rice	Y
8	Stanford	Y
9	Case Western	Y
10	Johns Hopkins	

From: World Technology Evaluation Center Report: International Assessment of Research and Development in Stem Cells for Regenerative Medicine and Tissue Engineering, MAR 2008

Top Publishing US Scientists (2001-2007)

Stem Cells for Regenerative Medicine and Tissue Engineering

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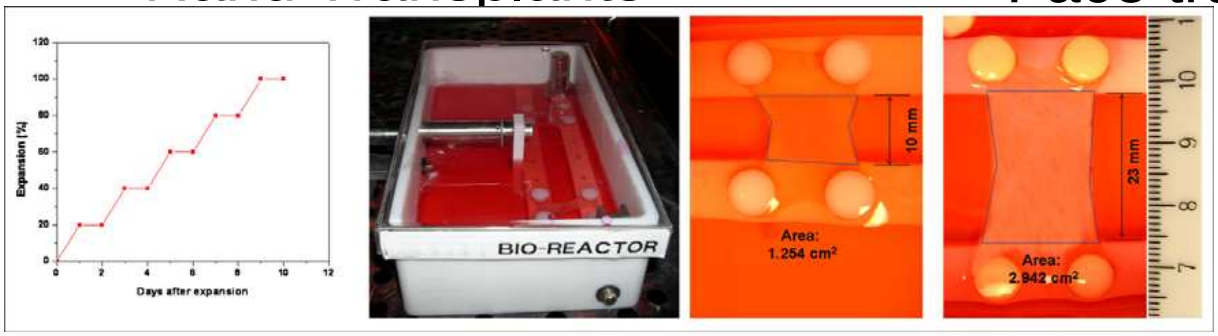
US Rank	Researcher	In AFIRM
1	David Kaplan	Y
2	Rocky Tuan	
3	Robert Langer	Y
4	Gordana Vunjak-Novakovic	
5	Johnny Huard	Y
6	Michael Longaker	Y
7	Jeffrey Gimble	
8	Joseph Vacanti	Y
9	Anthony Atala	Y
10	Antonios Mikos	Y

From: World Technology Evaluation Center Report: International Assessment of Research and Development in Stem Cells for Regenerative Medicine and Tissue Engineering, MAR 2008

AFIRM: clinical trials scheduled for FY 10

Hand Transplants

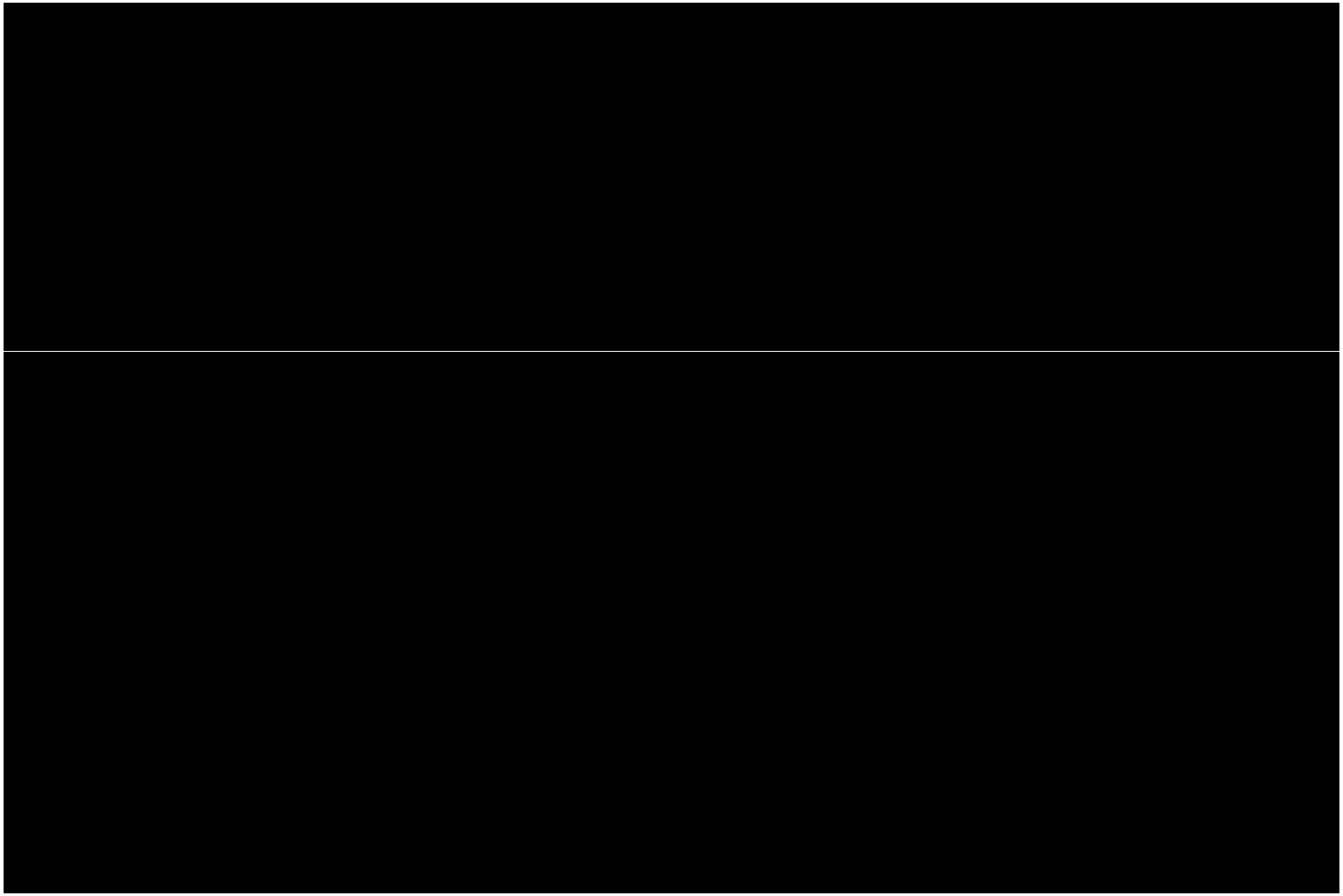
Face transplants



Skin Graft Stretching

www.afirm.mil

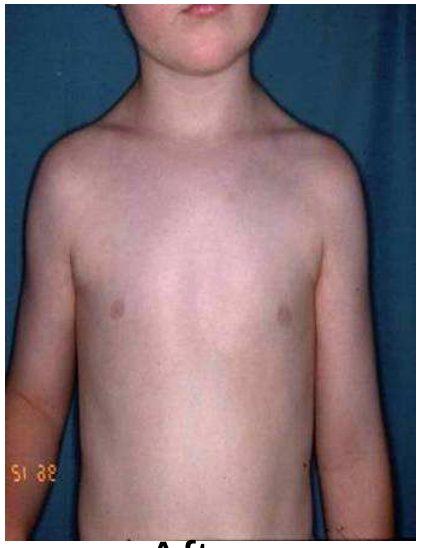
Josh Maloney
1st AFIRM Hand Transplant



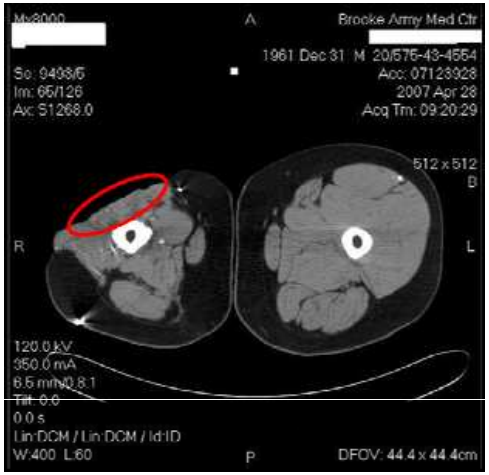
AFIRM: clinical trials scheduled for FY 10

Cell spraying in place of skin grafting for burn patients (ReCell)

Before

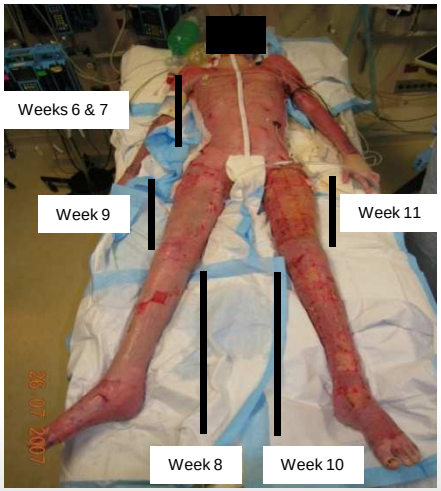


After



Using Extracellular matrix to regrow lost muscle tissue.

Autologous engineered skin grafts



Not shown: Fat injections to reduce burn scars and increase mobility.

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ReCell Kit

Cultured Epithelial Autograft (ReCell)

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ReCell: Scar Revision

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